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Short title: Feedback Loop Transitions in the PINE Network

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Abstract

Background

Biological pathways underlying major depressive disorder (MDD) can be viewed as systems biology networks. The psycho-immune-neuroendocrine (PINE) network comprises central nervous, immune, endocrine and autonomic systems, integrating biological mechanisms of MDD. Such networks exhibit recurrent motifs with specific functions, including positive and negative feedback loops, and are subject to critical transitions, influenced by feedback loop transitions (FLTs).

Aims

We aim to identify critical feedback loops and their FLTs, as well sentinel network nodes (SNNs), key network nodes that drive FLTs, within the PINE network. Examples of biomarkers are provided which may reflect early warning signs of impending critical transition to MDD.

Results

Disruption of homeostatic feedback loops reflects the physiological transition to MDD. Putative FLTs are identified within hypothalamic-pituitary-adrenal (HPA) and sympathetic-parasympathetic axes, the kynurenine pathway, gut function and dysbiosis.

Conclusions

Progression from health to disease is driven by FLTs in the PINE network, which is likely to undergo changes characteristic of system instability. Biomarkers of system instability may effectively predict the critical transition to MDD.

1. Introduction

1.1 Major Depression in the Context of Systems Biology and Biological Networks

Major Depressive Disorder (MDD) is recognised as one of the most common and debilitating diseases worldwide (Belmaker & Agam, 2008; Charlson, Stapelberg, Baxter, & Whiteford, 2011). The lifetime prevalence of MDD is approximately 17% within the population globally, underpinning tremendous secondary costs to society (Kessler, Chiu, Demler, & Walters, 2005; Wang, Simon, & Kessler, 2003). MDD is one of the largest causes of morbidity worldwide (Vos & Mathers, 2000) and is currently ranked third in terms of global burden of disease (World Health Organization, 2008). It is the leading cause of neuro–psychiatric disability (Lopez & Mathers, 2006) and has been predicted to be among the three leading causes of burden of disease worldwide by 2030 (Mathers & Loncar, 2006).

There is a growing body of research into the biological pathways that mechanistically underlie MDD. In recent years these paths have increasingly been viewed as biological networks (Headrick et al., 2017; Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2011; Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2015; Sterling & Eyer, 1988). Stapelberg et al. (2015) proposed the psycho-immune-neuroendocrine (PINE) network model to better understand and integrate putative biological mechanisms for MDD, and also how MDD is related to other general medical conditions. The PINE network model is comprised of central nervous system (CNS), immune, endocrine and autonomic networks. These constituent networks have been previously described individually or in combination. For example, networks modulating immune, autonomic and endocrine functions have been described as the neuroendocrine-immune network (Freier, 1990), the immune-neuroendocrine network (INEN) (Correa et al., 2007), or the neuroendocrine-immune axis (Homo-Delarche & Dardenne, 1993). The integrative term "psycho-neuroimmunology" has also been used to describe the study of biological mechanisms which underlie behavior and

mood in MDD (Ader, 2000).

The recognition of networks in biology and adoption of systems biology approaches have become widespread, and are pertinent to the study of MDD. Many fields of biology increasingly employ high-throughput experimental methods to generate greatly increased volumes of experimental data that are inherently complex and interconnected (Gehlenborg et al., 2010). The inter-connectedness of complex biological interactions has driven a paradigm shift from reductionist methodologies to the more holistic and inclusive paradigm of systems biology: the integrated and holistic analysis of complex interacting biological pathways or networks (Kirschner, 2005; Noorbakhsh, Overall, & Power, 2009). Emerging fields of high-throughput, data-rich biology, which employ systems biology and network approaches, have become identified by the suffix "ome" or "omics". Familiar fields of research in this area include genomics, proteomics and metabolomics (Hogenesch & Ueda, 2011).

An important characteristic of biological networks is their ability to maintain their stability, in other words their propensity to self-regulate or maintain homeostasis (Bashan, Bartsch, Kantelhardt, Havlin, & Ivanov, 2012; Stapelberg et al., 2015; Sterling & Eyer, 1988). Systems biology aims to construct coherent models that predict how biological systems might respond to different perturbations (Gracey, 2007). An important element of complex biological system responses to perturbation is the feedback loop (Kitano, 2004). Complex biological networks have recurrent structures, which achieve specific regulatory or other functions. Structures such as positive and negative feed-forward and feed-back loops are recognizable across different biological (and other) networks, and are known as 'network motifs' (e.g. Alon, 2007; Milo et al., 2002; Prill, Iglesias, & Levchenko, 2005). Negative feedback is more common and widespread in biology than positive feedback. Negative feedback broadly acts to stabilize, whereas positive feedback amplifies system perturbations and triggers changes in state, which may lead to system instability. Dysfunction within

negative feedback loops can impair homeostasis, while transition from negative to positive feedback may induce profound changes in the state of the system.

1.2 Feedback Loops, Sentinel Network Nodes and Critical Transitions in the Psycho-Immune-Neuroendocrine Network

It has previously been argued that the complex network of physiology underlying MDD undergoes a critical transition from a healthy PINE *physiome* to a PINE *pathome* with the onset of MDD (Stapelberg et al., 2015). The physiology underlying MDD consists of multiple interlocking pathways (e.g. see Stapelberg et al., 2011; Stapelberg et al., 2015, Headrick et al., 2017) and we assert here that the complex physiology underlying critical transition to MDD involves multiple feedback loop transitions (FLTs) from negative to positive feedback. We propose that these FLTs destabilise the PINE network, creating an unstable pre-disease state which can be measured using biomarkers, and that the FLTs of multiple physiological regulatory loops leads to positive feedback loop dominance and critical transition of the PINE network to the pathological state of MDD.

Critical transitions are defined as the thresholds at which entire systems shift abruptly from one state to another (Scheffer et al., 2009) and complex systems exhibit tipping points at which minor perturbations can invoke critical transition to a new stable state (Veraart et al., 2012). While critical transitions generally occur at a 'whole-of-system' level, they are brought about by changes within constituent regulatory elements of that system (Kitano, 2004; Veraart et al., 2012). It has been put forward that disease manifests from a gradual deterioration of health (which is frequently reversible), through relatively sudden critical transitions that demark a definitive disease onset and are frequently irreversible (Chen, Liu, Li, & Chen, 2016; Li, Jin, Lei, Pan, & Zou, 2015).

The concept of critical transitions is related to network motifs and feedback

mechanisms within complex systems, including biological systems (e.g. An, Nieman, & Vodovotz, 2012). Critical transitions in complex systems are influenced by transitions in constituent feedback loops and shifts in dominance between negative *vs*. positive loops, a concept known as 'loop dominance' (Ford, 1999; Sterman, 2000). The relationships between systems, comprised of feedback loops, loop dominance and critical transition of a system are illustrated in Figure 1. One challenge in establishing detailed models of feedback loop dominance to describe system behaviour has been in defining loop dominance itself; and therefore establishing what makes a particular feedback loop dominant (Ford, 1999). One definition of loop dominance posits that "a loop that is primarily responsible for model behaviour over some time interval is known as a dominant loop." (Richardson & Pugh III, 1981, p 285).

System dynamics explains how the structure or architecture of a system drives its behaviour (Ford, 1999). This concept is related to the idea that the existence of structural and dynamic properties of systems are largely independent of the detailed individual pathways or mechanistic components constructing the system (e.g. Mikulecky, 2001) - that is, they have emergent properties. Describing and linking feedback loops and shifts in loop dominance within a system to behaviour patterns, especially critical transitions, is vital in understanding system behaviour, and requires analysis to identify dominant loops in the system (Ford, 1999). Indeed, a key goal of system dynamics is understanding how the feedback structure of a system contributes to its dynamic behaviour (Richardson, 1995).

The concept of critical transitions in physiological systems is illustrated briefly by the well-studied mechanisms of insulin resistance. A negative feedback loop, such as that governing homeostatic control of blood glucose levels, can be gradually disrupted by increasing resistance to insulin. Insulin resistance itself is complex and can be caused by numerous defects in the insulin signaling cascade (e.g. Kadowaki et al., 2006), although

disruption to glucose homeostasis can be illustrated in relatively simple terms. Increased blood glucose triggers insulin secretion by pancreatic ß-cells, and insulin signaling mechanisms cause glucose to be transported into cells, lowering blood levels. Insulin resistance causes less glucose to be transported into cells, which drives increased insulin production. While there is still an inhibitory effect from insulin, this diminishes with increasing insulin resistance. There is a point at which the net inhibitory effect reaches zero, which represents the FLT of this system. From here, the system enters into a positive feedback loop with more insulin being produced, driving further insulin resistance and elevation of blood glucose. This is a relatively simple example, and it should be recognised that the insulin system is interleaved with other physiological systems, forming a complex network (e.g. Taniguchi, Emanuelli, & Kahn, 2006).

PINE physiology is viewed as a network, constituted of nodes and edges. Nodes can be genes, proteins or biochemical and physiological processes that are connected to multiple other system elements via edges (e.g. McNally, 2016). Nodes with greater numbers of connections have greater regulatory potential, while other nodes can serve as control elements in physiological feedback loops regardless of their interconnectivity. Taniguchi et al. (2006) defined 'critical nodes' in signalling networks that are essential for a receptor-mediated signal, have unique biological roles within a signalling network, are highly regulated (positively and negatively), and form one or more junctions for potential crosstalk with other signalling systems. Transitions around such nodes will have profound and system-wide effects on the transition from health to disease. Wittenborn, Rahmandad, Rick, and Hosseinichimeh (2016) identified 'candidate stock variables' that they identified as regulating the strength and dynamics of the reinforcing loops they describe. We also seek to identify nodes that are critical to FLTs in the described regulatory loops. These may not meet the criteria for 'critical nodes' as defined by Taniguchi et al. (2006), but represent nodes that

are likely to directly drive FLTs (thus ultimately contributing to system-wide transitions) and we have named these sentinel network nodes (SNNs).

The first aim of this paper is to identify important feedback loops in the PINE network based on current knowledge. Negative and positive feedback loops within the PINE physiome are defined, and it will be shown how loss of negative feedback and creation of positive feedback - evolution of a FLT - can lead to positive feedback loop dominance in the PINE network and thereby drive critical transition to MDD. We propose that by monitoring shifts in feedback loop dominance with biomarkers designed to detect early warning signs of critical transitions (Scheffer et al., 2009), particularly around SNNs, a global transition to MDD might be detectable and indeed predictable. We outline examples of measurable biomarkers related to critical transition of the PINE network, based on shifts in the behaviour of feedback loops. These biomarkers are hypothesized to predict how patterns of critical transition will collectively change between healthy individuals and people with MDD, and how they may therefore serve as a screening tool for the onset of MDD. One example is provided for each early warning sign of critical transition, as proposed by Scheffer et al. (2009).

Biomarkers can be defined as specific biological features, or any substance, structure, or process that can be measured in the body to aid in distinguishing the presence or absence of a specific disease (Schmidt, Shelton, & Duman, 2011; Strimbu & Tavel, 2010). While there have been advances in the study of biomarkers in MDD, efforts to validate MDD biomarkers have been challenging and a quantitative clinical test for MDD remains elusive (Kennedy et al., 2012; Lakhan, Vieira, & Hamlat, 2010). Clinical utility is governed by multiple factors, notably their mechanistic linkage to MDD pathology (which may be difficult to elucidate), sensitivity and specificity relative to other psychological disorders, and dependence on complicating factors such as sex, age, diet and activity. Pathological

heterogeneity evident in MDD also remains a critical factor limiting the applicability of biomarkers, while technical and economic factors or constraints are important in determining broader utility. Additional to blood and cerebrospinal fluid (CSF) biomarkers, and genomic, transcriptomic, proteomic and metabolomic analytical approaches, modalities such as neuroimaging and electroencephalographic (EEG) analyses offer some potential. For example, shifts in EEG patterns are evident in depression, however despite recent encouraging reports (e.g. Lee, Kan, Croarkin, Phang, & Doruk, 2018) there remains significant heterogeneity in findings (in part reflecting pathological heterogeneity), and broader utility in MDD remains to be established. Despite considerable research and testing there is no consensus on which biomarkers are sufficiently sensitive and specific to be employed clinically.

In recent times there has been recognition of the importance of examining groups or panels of biomarkers, rather than investigating individual markers, in relation to chronic stress (Juster, McEwen, & Lupien, 2010) or MDD (Domenici et al., 2010; Strawbridge, Young, & Cleare, 2017). It has been recommended that large groups of biomarkers across different modalities be studied in concert, and that advanced mathematical modelling, machine learning and pattern recognition methods be used to analyze such biomarker groupings and their relation to diseases such as MDD (Kennedy et al., 2012; McEwen, 2015). Groups of markers of feedback loop behaviour, e.g. shifts in feedback loop dominance, may cumulatively offer a unique capacity to monitor the emergence of unstable pre-disease states, or presage a critical transition. We highlight biomarkers directly linked to disease mechanism, based on connections and mechanisms within the theoretical PINE network (Stapelberg et al., 2015).

There is a wider literature examining networks in the context of MDD. For example Borsboom and Cramer (2013), provide a network analysis of symptoms of MDD and

generalized anxiety disorder (GAD) based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and correlations based on National Comorbidity Survey Replication data. Wittenborn et al. (2016) present networks that combine psychological, cognitive, social and biological factors. While they identify reinforcing and negative feedback in their models, the concept of feedback loop transitions are not described. While these examples illustrate that network models of MDD can incorporate a wide range of nodes related to psychological symptoms or social factors, we have restricted this paper to physiological mechanisms only.

2. Results

2.1 Endocrine-Related Feedback Loops: Glucocorticoid Receptors, the Glucocorticoid Negative Feedback Loop and Glucocorticoid Resistance in Major Depression

The hypothalamic pituitary adrenal (HPA) axis is a well-studied regulatory system that is crucial to energy regulation in the body to meet metabolic demand, through control of glucose availability among other mechanisms (Pecoraro et al., 2006). It is also intimately involved in the response to stress (Stapelberg et al., 2015), and feedback mechanisms exist at multiple levels. The principal HPA axis pathway starts with the hypothalamus in the central nervous system (CNS) and ends with the secretion of glucocorticoids such as cortisol into the bloodstream, a pathway subject to negative feedback control and which can be viewed as cyclical in that it is self-regulating (Figure 2A).

[Figure 2A could be placed here]

The synthesizing motor neurons of the paraventricularnucleus (PVN) in the hypothalamus release corticotropin-releasing hormone (CRH) into the portal vasculature of the median eminence (Fink, 2010; Pecoraro et al., 2006). CRH stimulates adrenocorticotropic hormone (ACTH) production in the glandular corticotrope cells of the anterior pituitary

gland, and its release into the bloodstream (Pecoraro et al., 2006). Circulating ACTH stimulates the production of glucocorticoids (e.g. cortisol) in the adrenal cortex, which enter the systemic circulation and can cross the blood brain barrier to act in the CNS. Glucocorticoids act by binding to glucocorticoid receptors (GRs) in target tissues, including the hypothalamus. GRs in the hypothalamus trigger a reduction of CRH production and secretion, which negatively feeds back on the HPA axis pathway, ultimately slowing the production of cortisol and other glucocorticoids (e.g. O'connor, O'halloran, & Shanahan, 2000; Tsigos & Chrousos, 2002). In addition, glucocorticoids themselves inhibit both the synthesis and release of ACTH (Axelrod & Reisine, 1984).

However, the feedback loops that involve GRs are more complex, since glucocorticoids also bind to mineralocorticoid receptors (MR). The MRs are expressed in the kidneys, heart and intestine, and also in limbic brain regions including the hippocampus. They have a higher affinity for glucocorticoids than GRs (Rupprecht et al., 1993) and are thus more completely occupied by basal levels of corticosteroid secretion under normal physiological conditions (Anacker, Zunszain, Carvalho, & Pariante, 2011a). Conversely, relatively low affinity GRs (Rupprecht et al., 1993) require high glucocorticoid concentrations for full activation and subsequent dampening of HPA axis activity. Both MRs and GRs are required to drive the HPA axis negative feedback loop, thus the ratio of MR/GR expression and activation is important in MDD (Juruena et al., 2006). Under normal physiological conditions, the MR/GR activity ratio is high since MRs are more fully occupied than GRs (Anacker et al., 2011a). Indeed, it has even been suggested MR activation alone may largely account for behavioral reactivity to acute and brief stressors (Holsboer, 2000). However chronic stress, which can lead to MDD, causes a sustained elevation in glucocorticoid production, and thus more complete GR binding and a reduced MR/GR ratio (Holsboer, 2000). Importantly, the effects of combined MR and GR activation with chronic

stress and glucocorticoid release are distinct from those of GR or MR activation alone (Anacker et al., 2013a), and may be maladaptive, for example inhibiting neurogenesis. Chronically elevated glucocorticoids also induce initial MR desensitization and subsequent GR desensitization and glucocorticoid resistance (Holsboer, 2000; Pace, Hu, & Miller, 2007; Tsigos & Chrousos, 2002). Glucocorticoid resistance is in effect a reduced response to increased ligand levels, involving mechanisms which inhibit glucocorticoid bioavailability, GR expression and signaling, thereby suppressing negative feedback effects previously driven by GR activity.

With loss of the negative feedback loop that normally regulates glucocorticoid serum concentrations, glucocorticoid levels continue to rise with no corresponding dampening of the immune response or de-activation of the HPA axis. This is illustrated in Figure 2B. A regulatory negative feedback loop is thus transitioned to a positive (or feedforward) loop, dysregulating the physiological cycle to promote pathology. Glucocorticoid and thus HPA axis dysregulation is implicated in several pathways which lead to MDD, particularly immuno-inflammatory paths.

[Figure 2B could be placed here]

2.1.1 Mechanisms of Glucocorticoid Resistance - Limitation of Glucocorticoid Availability

Three mechanisms determining the intracellular availability of glucocorticoids are implicated in glucocorticoid resistance. The first involves multidrug resistance P-glycoprotein (MDR), which acts as an efflux pump, removing intracellular toxins in organs including the adrenal glands, kidneys, liver, gut, and brain. The MDRs in the blood-brain barrier endothelium extrude cortisol and other glucocorticoids from these cells, effectively limiting cortisol availability at intracellular GRs (Silverman & Sternberg, 2008). Acute

inflammatory responses down-regulate MDR function, increasing the availability of glucocorticoids and thereby permitting the feedback dampening of inflammation. Conversely, chronic inflammation results in up-regulation of MDR expression, limiting cortisol availability and contributing to cortisol resistance (Silverman & Sternberg, 2008).

The second mechanism relates to corticosteroid binding globulin (CBG), which binds ~90% of circulating glucocorticoids. Enhanced CBG expression thus limits glucocorticoid bio-availability, restricting movement from capillaries into cells and potentially contributing to glucocorticoid resistance (Silverman & Sternberg, 2008). Pro-inflammatory cytokines (particularly IL-6) reduce CBG expression, increasing glucocorticoid availability and thus dampening inflammation (Silverman & Sternberg, 2008). However it has been argued that in chronic inflammation changes in CBG expression may reduce glucocorticoid availability (Silverman & Sternberg, 2008, 2012).

The third mechanism implicates the two isoforms of 11β-hydroxysteroid dehydrogenase (11β-HSD) in glucocorticoid resistance. The 11β-HSD-1 isoform converts glucocorticoids to their biologically active form, while 11β-HSD-2 converts them to intermediate inactive forms (e.g. cortisol to cortisone). In an acute inflammatory response, pro-inflammatory cytokines such as TNF-α and IL-1β promote 11β-HSD-1 up-regulation and 11β-HSD-2 down-regulation in several cell types, favouring active glucocorticoid signalling and negative feedback that subsequently dampens inflammation (Figure 2A). However it has been proposed that in chronic inflammation, the levels of both 11β-HSD isoforms may be altered to increase inactive relative to active glucocorticoids, for example by increasing 11β-HSD-2 conversion to inactive forms which do not trigger a dampening of inflammation, thus limiting availability of active glucocorticoids and thus contributing to glucocorticoid resistance (Silverman & Sternberg, 2008, 2012).

2.1.2 The HPA Axis and Immune Regulation: Glucocorticoid Receptors and Nuclear Factor Kappa-B in Immune-Related Feedback Loops

The balance between glucocorticoid and nuclear factor kappa-B (NF-κB) signaling is an additional and important mechanism influencing glucocorticoid resistance (reviewed in McKay & Cidlowski, 1999), linked to immuno-regulatory negative feedback control. The immune system can defend the body from infection by maintaining a dynamic balance between pro-inflammatory (e.g IL-1, IL-2, IL-6, and TNF-α) and anti-inflammatory mediators (e.g. IL-4, IL-10 and IL-13). This balance shifts towards a pro-inflammatory state when the immune system is challenged, while regulatory mechanisms appropriately dampen this response to limit damage to the body (Eskandari & Sternberg, 2002; Olofsson, Rosas-Ballina, Levine, & Tracey, 2012). The balance between pro- and anti-inflammatory cytokines is regulated in part by the HPA axis. Pro-inflammatory cytokines such as IL-6 stimulate the HPA axis and CRH, in particular via the hypothalamus and the amygdala (Besedovsky & Rey, 1996; Raison, Capuron, & Miller, 2006), driving glucocorticoid release. Glucocorticoids in turn feedback on the immune system to inhibit pro- and promote anti-inflammatory cytokine production, including annexin-1, SLPI, IL-10 and the NF-κB inhibitor IκB-α, though these may be differentially expressed in different cell types (Barnes, 2006). These actions create a regulatory negative feedback loop to dampen inflammation. GRs and NF-κB are central to this immune regulatory feedback loop, which in turn influences glucocorticoid resistance.

GRs and NF-κB are inducible transcription factors with opposed functions in immune and inflammatory control. The master regulator NF-κB, together with pro-inflammatory transcription factors such as activator protein-1 (AP-1), mediate pro-inflammatory cytokine production (Barnes, 2006; McKay & Cidlowski, 1999). GRs function as ligand-dependent transcription factors to down-regulate cytokine gene expression: GR binding at

glucocorticoid response elements (GREs) in promoter regions of corticosteroid-responsive genes can both suppress transcription of (transrepress) inflammatory system elements, including cytokines (IL-12, TNF-α, interferon-γ), adhesion molecules and inflammatory enzymes, and promote transcription of (transactivate) anti-inflammatory mediators such as IL-10 (Barnes, 2006; Sternberg, 1997). These regulatory actions may be influenced by physical interaction between GRs and NF-κB, which function as mutual transcriptional antagonists. Indeed, modulation of glucocorticoid action is a key role of NF-κB (McKay & Cidlowski, 1999). In this way increased NF-κB activity, activated by stressors such as viral infection or oxidants (Baeuerle & Baltimore, 1996), and pro-inflammatory cytokines (DiDonato, Hayakawa, Rothwarf, Zandi, & Karin, 1997), may promote glucocorticoid resistance when chronically activated (e.g. Bantel, Schmitz, Raible, Gregor, & Schulze-Osthoff, 2002).

Additional to this classical genomic signaling, feedback control of non-genomic immune signaling may be disrupted in transition to MDD, including cellular immunity. T and natural killer (NK) cell mediated immune responses are negatively regulated by glucocorticoids (Chen, Jondal, & Yakimchuk, 2017), and there is growing evidence that these cells (influencing neuro-inflammation and -protection) are involved in MDD development (Miller, 2010). Abnormalities in both cell levels and functions are evident in MDD (Blume, Douglas, & Evans, 2011; Eyre, Stuart, & Baune, 2014; Miller, 2010). There is general support for impaired Th2, Th17 and NK cell maturation with depressive state, and a fall in regulatory T cell numbers that correlates inversely with monocyte inflammatory state (Grosse et al., 2016a; Grosse et al., 2016b). Circulating T and NK cells might thus serve as useful biomarkers - reduced regulatory T cell numbers in MDD are improved with anti-depressant therapy (though not necessarily predicting clinical outcome), whereas anti-depressant non-responders exhibit elevated cytotoxic T and NK cell levels (Grosse et al., 2016a). Abnormal

GR activity and glucocorticoid resistance may precipitate dysfunction in T cell maturation and function, worsening immune defense and risk of infection. Despite limited analyses in MDD, susceptibility to streptococcal infection is increased in children exposed to acute or chronic family stress (Meyer & Haggerty, 1962), low socioeconomic status increases respiratory infection in association with T cell telomere shortening (Cohen et al., 2013), and similar T cell senescence with early life adversity is linked to increased cytomegalovirus infection (Elwenspoek et al., 2017). T cells not only perform a surveillance function (Baruch & Schwartz, 2013), but regulate neurogenesis and neuroplasticity (Ziv & Schwartz, 2008), and protect against maladaptive behavioural responses (Lewitus et al., 2009). Removal of cortisol's inhibitory effects with evolving glucocorticoid resistance may permit maladaptive T cell responses to emerge, promoting neurodegeneration (Toben & Baune, 2015). This may involve both elevated pro-inflammatory T cells and reduced regulatory T cells and anti-inflammatory cytokines (Toben & Baune, 2015).

In summary, dysregulation of both genomic and non-genomic GR signaling arises with chronic stress, contributing to glucocorticoid resistance and disrupting a fundamentally important negative feedback loop that normally dampens inflammation. This leads to dominance of pro- over anti-inflammatory cytokines and signaling, driving further GR disruption and glucocorticoid resistance, and further pro-inflammatory outcomes: previously negative feedback control has become disrupted to the point of shifting to a positive feed-forward loop. This is illustrated in Figure 2B.

2.1.3 Dysregulated Expression and Feedback Control of Glucocorticoid Receptors

At a deeper mechanistic level, expression and (dys)regulation of the GR itself governs glucocorticoid signaling and resistance, contributing to transitions from health to MDD, shown in Figure 2C. Stapelberg et al (2015) described the PINE network transition from

health to pathology in terms of a stress-diathesis model. While discussion of genetic and epigenetic mechanisms for all physiological pathways described here is beyond the scope of this paper, expression of GR is presented as an example. Certainly, unravelling these mechanisms and their integration into network models can clarify processes of immuno-inflammatory dysregulation in transition to MDD, and reveal additional biomarkers of disease development and therapy. MDD is associated with declining expression of the GR gene (*NR3C1*) in the CNS (Webster, Knable, O'grady, Orthmann, & Weickert, 2002) and in circulating cells (Spindola et al., 2017), and with *NR3C1* variant expression in females (Sarubin et al., 2017). However, the mechanisms orchestrating tissue-specific GR expression and levels of the 2 prevalent isoforms - dominant GRα involved in gene transactivation and inhibitory GR - await further clarification (Turner et al., 2010). Increased GR expression has been suggested as a mechanism for glucocorticoid resistance, though generally low level expression across cells argues against such a role (Pujols et al., 2003). However, nuclear shuttling of GR via FK506 binding protein 51 (FKBP51) inhibits gene transactivation by active GRα shuttled via FKBP52 (Zhang, Clark, & Yorio, 2008). Thus, shifts in the FKBP51/52 rather than GRα/ ratio may be important in stress-dependent glucocorticoid resistance. This is consistent with associations between FKBP5 expression, glucocorticoid resistance and reduced coping behaviour, and FKBP5 gene variants and risk of affective disorders (Criado-Marrero et al., 2018).

These associations may reflect epigenetic control of GR and associated protein expression with chronic stress and MDD (Turner et al., 2010), though further work is needed to clarify these processes. It is increasingly clear *NR3C1* together with *BDNF* and *FKBP5* promoters are hypermethylated in MDD patients, with concordant reductions in *NR3C1* genes and *BDNF* and shifts in *FKBP5* variants (Roy, Shelton, & Dwivedi, 2017). Early life adversity, a major risk factor for psychopathology, is frequently associated with *NR3C1*

hypermethylation (Bustamante et al., 2016; Palma-Gudiel, Córdova-Palomera, Leza, & Fañanás, 2015). Childhood abuse (McGowan et al., 2009), parental loss (Tyrka, Price, Marsit, Walters, & Carpenter, 2012), and maternal depression (Oberlander et al., 2008) or separation (Weaver et al., 2004) are all associated with hypermethylation of a splice-variant promoter, which decreases total and *NR3C1* 1-F mRNAs (McGowan et al., 2009). The miRNA-dependent control of GR and FKBP expression may also be important in MDD, and warrants more extensive interrogation. For example, a miR-124 antagomir counters stress-dependent depressive behaviours and activates BNDF (Wang et al., 2017), and depression-like behaviour is associated with increased miR-124a and FKBP5 *vs*. reduced GR levels in the amygdala (Xu et al., 2017).

Post-translationally, GR signaling, feedback control and resistance are phospho-regulated (Ismaili & Garabedian, 2004) (Figure 2C). Links between GR phosphorylation and negative affectivity support utility as a potential biomarker, and its incorporation into the molecular signature of negative affective states (Jovicic et al., 2015). Stress, glucocorticoids and inflammatory cytokines, together with growth factors, sex hormones and other kinase modulators, modulate GR phosphorylation within a N-terminal domain region linked to cofactor binding and gene transactivation (Anacker et al., 2011b; Guidotti et al., 2013) (Figure 2C). Genomic signaling is promoted by Ser203 or Ser211 phosphorylation, which enhances nuclear translocation and transactivation, while Ser226 phosphorylation increases nuclear export and degradation of GRs and inhibits transactivation (Anacker et al., 2013b; Guidotti et al., 2013; Ismaili & Garabedian, 2004). GR turnover is highly dependent on phosphorylation, with receptor half-life greatly augmented in the absence of this control (Webster et al., 1997).

GR phosphorylation is modulated by FKBP51 and 52, and mediated by kinases including cytokine-induced c-Jun N-terminal kinases (JNKs), p38-MAPK, cyclin-dependent

kinases (CDKs) and GR inducible serum- and glucocorticoid-inducible kinase 1 (SGK1) (Ismaili & Garabedian, 2004; Miller et al., 2005). The FK506 binding proteins 51 and 52 (encoded by FKBP5 and 4) function with HSP90 as co-chaperones for inactive and active GRs, respectively (Criado-Marrero et al., 2018; Storer, Dickey, Galigniana, Rein, & Cox, 2011; Wang, Frederick, & Garabedian, 2002), and are linked to MDD pathogenesis (Simic et al., 2013b; Tatro et al., 2009). Lacking direct phospho-regulatory properties, FKBP51 and FKBP52 influence phosphorylation via ill-defined mechanisms to inhibit and promote GR signaling, respectively. The balance of FKBP51 and 52 expression, which also determines shuttling of inhibitory GR🚲*vs*. active GRα isoforms, thus modulates GR activation, translocation and gene transactivation, with imbalances contributing to glucocorticoid resistance (Bourke et al., 2013; Guidotti et al., 2013). Conversely, Ser226 phosphorylation by JNK (Avenant, Kotitschke, & Hapgood, 2010; Chen et al., 2008; Itoh et al., 2002) or p38-MAPK (Mercado et al., 2012) increases nuclear GR export and reduces transcriptional activity, while p38-dependent Ser203 phosphorylation may also maintain GRs in an inactive state (Bouazza et al., 2014). Other post-translational control is sensitive to phosphorylation: JNK-dependent phosphorylation at Ser246 (226 in human GRs) enhances sumoylation to suppress transactivation (Beck, De Bosscher, & Haegeman, 2011; Davies et al., 2008), and ligand-mediated proteasomal GR degradation requires phosphorylation-dependent lysine ubiquitination (Beck et al., 2011; Webster et al., 1997).

Dephosphorylation is also altered with stress and inflammation. The dephosphorylation of GR serines 203, 211 and 226 may be mediated by PP5 (Bouazza et al., 2012; Ismaili & Garabedian, 2004; Silverstein et al., 1997; Wang, Chen, Kono, Dang, & Garabedian, 2007), which also acts as co-chaperone with HSP90 in GR shuttling, and is induced on GR activation to reduce Ser211 phosphorylation and inhibit signaling (Bouazza et al., 2012) (Figure 2C). Down-regulating PP5 enhances GR phosphorylation and

transactivation (Bouazza et al., 2012), increasing gene expression without affecting GR binding (Zuo et al., 1999). Dephosphorylation of upstream kinases targeting the GR also inhibits GR phosphorylation, including JNK dephosphorylation via protein phosphate 2A, protein tyrosine or dual specificity protein phosphatase activities.

The importance of phospho-regulation is reflected in the neuroplasticity effects of BNDF, dysregulation of which is implicated in MDD (Duman, Heninger, & Nestler, 1997; Hashimoto, 2013; Hashimoto, Shimizu, & Iyo, 2004). Neuroplasticity induced via the BNDF receptor (Trk🚲) involves essential GR phosphorylation and transactivation of plasticity genes (Arango-Lievano et al., 2015; Lambert et al., 2013), as does anti-depressant mediated neurogenesis (Anacker et al., 2011b). Neurogenesis outcomes may involve distinct effects of low sensitivity GRs *vs*. higher sensitivity MRs: normally low cortisol levels may act via MRs to increase hippocampal progenitor cell proliferation and differentiation into astrocytes, high cortisol levels inhibit proliferation via GRs, and combined GR and MR activities reduce neurogenesis into microtubule-associated protein 2-positive neurons and doublecortin-positive neuroblasts (Anacker et al., 2013a). Impaired neurogenesis with chronic stress may thus involve inhibitory effects of combined MR/GR signaling (reduced MR/GR ratio), and increased GR phosphorylation via GR inducible SGK1 and other kinases (Anacker et al., 2013b), leading to MR and GR desensitization and resistance (Holsboer, 2000).

As outlined in Figure 2C, phospho-regulation of GRs thus involves a balance between stimulatory (eg. glucocorticoid, BDNF) and inhibitory (eg. inflammatory cytokine) pathways. Negative feedback control includes GR transactivation of kinase inhibitors (eg. CDK inhibitor proteins), upstream triggers of kinase pathways (eg. anti-inflammatory cytokines) (Anacker et al., 2011b), counter-regulatory phosphatase proteins (eg. PP5), and inhibitory FKBP51. With chronic stress and inflammation this balance is increasingly shifted towards inhibitory phosphorylation via JNK and p38-MAPK. Coupled with initial GR-dependent

induction of PP5, kinase inhibitors and FKBP51, these changes induce glucocorticoid resistance, opening the feedback loop to exaggerate inflammatory responses, impair neurogenesis and promote system transitions in the path to MDD. Elevated cortisol levels in MDD do correlate with GR Ser226 phosphorylation (Simic et al., 2013), and nuclear GR Ser226 phosphorylation correlates with depressive symptoms in females (not males) (Simic et al., 2013a). Increased FKBP5 gene and FKBP51 protein are also observed in MDD (Simic et al., 2013b; Tatro et al., 2009), with hippocampal levels elevated in animal stress models, though again in females and not males (Bourke et al., 2013). Such sexually dimorphic outcomes are congruent with sex-specificity of GR phospho-regulation (Brkic et al., 2017). For example, lipolysaccharide (LPS) induced sickness behaviour is associated with increased GR phosphorylation, nuclear translocation and FKBP expression in females *vs*. reductions in males. This is important in light of evidence variations in the GR gene (*NR3C1*) are linked to MDD in females but not males (Sarubin et al., 2017), collectively suggesting a more dominant role for GR signalling in females than males. Sexual dimorphisms in MDD and underlying pathophysiology (Cosgrove, Mazure, & Staley, 2007; Goel, Workman, Lee, Innala, & Viau, 2014; Kessler, 2003; Nolen-Hoeksema, 1987) are a fundamentally important though complicating factor, just as existence of multiple MDD sub-types complicates interpretation and limits the utility of biomarkers.

In summary, disruption of GR-available glucocorticoid levels, interactions between GR and NF-kB, and shifts in post-translational and epigenetic control of GRs lead to changes in both genomic and non-genomic signalling (all influenced in turn by genetic background), collectively underpinning glucocorticoid resistance and contributing to transition or reversals in feedback control (see Figure 2). This disruptive FLT impacts humoral and cellular immunity and increases levels of CNS inflammatory mediators, leading to what has been termed 'sickness behavior' (Dantzer, 2009; Dantzer, O'Connor, Freund, Johnson, & Kelley,

2008; Reichenberg et al., 2001), a behavioural response to infection or inflammation prompting conservation and redirection of energy for recovery. Symptoms include loss of appetite, lethargy and withdrawal from physical and social environments (Dantzer, 2009). These may reflect a normal and beneficial response to infection, an appropriate shift in behavioural priorities (Dantzer, 2009) such that the organism rests and recovers, rather than engaging in conflicting energy-demanding tasks. However, these also represent neurovegetative symptoms of MDD (Association, 2013), an overlap suggesting sickness behaviour is a subset of depressive symptomatology, driven by the low-grade pro-inflammatory state apparent in MDD (Stapelberg et al., 2015). Dantzer (2009) argues that sickness behaviour can become pathological when occurring in the absence of an infective cause or when exaggerated in intensity or duration. This appears to be the case in MDD, with the mechanisms detailed above and the following descriptions of changes in gut biome and permeability and the kynurinine pathway providing examples of shifts in immuno-inflammatory regulation from negative to positive feed-forward states.

2.2 Immune-Related Feedback Loops: The Gut Microbiome and Gut Permeability Positive Feedback Loop

The human digestive tract harbors a complex community of microorganisms comprising some 40000 species of bacteria (weighing between 1 and 2 kg) that provide important host benefits, including ability to break down indigestible dietary polysaccharides (Foster & Neufeld, 2013). There are tradeoffs in maintaining what is normally a beneficial symbiosis for host and microbiome: large quantities of bacteria must be kept in close proximity to a metabolic system that can be overwhelmed and destroyed by them. A balance is maintained by stratification (minimizing direct contact between gut microbiota and the epithelial cell surface) and compartmentalization (confining the microbiome to intestinal sites

that limit exposure to the systemic immune compartment) (Hooper, Littman, & Macpherson, 2012). If gut microbiota, or associated microbial molecules such as LPS, do cross the gut wall and enter the blood, they stimulate an immune response which maintains compartmentalization. However, this control may be disrupted with excess or chronic passage of luminal LPS and other bacterial molecules across the gut wall (as a result of altered biome or permeability), transitioning to feed-forward control and promotion of pro-inflammatory state.

Raised blood concentrations of LPS have been linked to specific symptoms of MDD in animal models (e.g. Dantzer et al., 2008) and human studies (e.g. Wright, Strike, Brydon, & Steptoe, 2005). These symptoms include low energy and fatigue, loss of appetite, sleep disturbance, loss of sex drive and anhedonia, consistent with sickness behavior (Dantzer, 2009; Dantzer et al., 2008; Reichenberg et al., 2001) and identical to neurovegetative symptoms and anhedonia observed in MDD (Dantzer, 2009; Stapelberg et al., 2015). Normally, the intestinal epithelial barrier (IEB) allows luminal fluid and nutrients to cross the intestinal wall while limiting passage of LPS and other bacterial products (Mass, Kubera, & Leunis, 2008). However, increased levels of pro-inflammatory cytokines (e.g. interferon-γ, IL-6) promote IEB permeability to large molecules such as LPS (Chavez, Menconi, Hodin, & Fink, 1999; Clark, Hoare, Tanianis-Hughes, Carlson, & Warhurst, 2005; Yang et al., 2003), with increased serum LPS promoting further pro-inflammatory cytokine release (Dantzer et al., 1999; Maes, Mihaylova, & Leunis, 2007). This in turn leads to further IEB permeabilization to LPS and other bacterial macromolecules, creating the positive feedback loop summarised in Figure 2B. The permeability of the IEB thus represents a critical node, or determinant of feedback control transition - beyond a permeability threshold, passage of bacterial molecules trigger a self-propagating pro-inflammatory response (inflammation-dependent permeabilization drives up LPS levels, thus further inflammation and

permeabilization). This transition in feedback control (FLT) of barrier function is in turn related to transition in feedback within the 'HPA-gut axis'.

CRH plays a key role in gut function, increasing motility and secretion (Taché & Bonaz, 2007). Increased gut motility can over time change the composition of the gut microbiome (Quigley, 2011), with biome changes impacting permeability (Tremaroli & Bäckhed, 2012), and thus circulating levels of LPS and molecules that up-regulate pro-inflammatory mediators. These changes lead in turn to increased CRH levels, reflecting a positive feedback loop involving the gut microbiome. Thus, the composition of the gut microbiome, determining IEB permeability, is a key determinant of regulatory transitions and contributes to a system-wide critical transition to MDD. Feedback loop transition is further promoted by the effects bacterial toxins on glucocorticoid resistance, impairing GR function and GR transactivation (Silverman & Sternberg, 2012). Since glucocorticoid resistance increases CRH secretion, reflecting loss of negative feedback control, transitions in feedback control of glucocorticoid signalling, gut biome and permeability potentiate each other, arguably driving positive feedback loop dominance and critical transition to MDD.

2.3 Immune-Related Feedback Loops: The Kynurinine Pathway Negative Feedback Loop and the Astrocyte-Microglia Ratio

High systemic levels of pro-inflammatory cytokines can induce a pro-inflammatory milieu within the CNS. The kynurinine pathway (KP) is central to immune modulation throughout the body, including the CNS where the pathway is facilitated by microglia. The KP is implicated in negative feedback control of inflammation, responding to pro-inflammatory state and inhibiting inflammation via its metabolites. However, the ratio of KP metabolites in the CNS can be altered with chronic stress to ultimately promote pro-inflammatory changes, transitioning to an abnormal positive feedback loop. With chronic

stress, a pro-inflammatory milieu in the CNS disrupts glial populations, resulting in predominance of microglia and depletion of astrocytes (reviewed in Stapelberg et al., 2015). This amplifies the KP positive feedback loop, which has multiple effects, including disruption of CNS serotonergic function and neural health, and inhibition of hippocampal neurogenesis, all precursors to MDD.

Microglia are critical in functionally supporting the central KP (Müller & Schwarz, 2007). Microglia produce indoleamine 2,3-dioxygenase (IDO) which converts tryptophan to kynurenine (McNally, Bhagwagar, & Hannestad, 2008; Müller & Schwarz, 2007). The activity of IDO, thus of the KP itself, is stimulated by pro-inflammatory cytokines such as interferon-γ, TNF-α, IL-1 and IL-2 (reviewed in Mándi & Vécsei, 2012). As shown in Figure 3A, kynurenine is further converted to kynurenic acid and 3-hydroxykynurenine, with the latter converted to quinolinic acid (Müller & Schwarz, 2007).

[Figure 3A could be placed here]

The KP and its metabolites are important in the balance between neurotoxicity and neuroprotection in the CNS (Allison & Ditor, 2014). Kynurenic acid dampens inflammation by inhibiting production of the key mediator TNF-α (Mándi & Vécsei, 2012). The inhibition of TNF-α production has a neuroprotective function, as TNF-α provokes glutamate-induced neuronal cell death (Zou & Crews, 2005) and neuronal death with stroke and other CNS insults. Kynurenic acid acts as an NMDA antagonist (Stone & Perkins, 1981), blocking TNF-α potentiation of glutamate neurotoxicity (Zou & Crews, 2005). Other KP metabolites, such as 3-hydroxykynurenine and quinolinic acid, have neurotoxic effects. For example, quinolinic acid acts as a selective NMDA receptor agonist, driving glutamate-mediated neurotoxicity (Stone & Perkins, 1981) and thus functionally opposing the effects of

kynurenic acid itself. The balance between kynurenine transamination to kynurenic acid *vs*. hydroxylation and subsequent metabolism to quinolinic acid is thus a determinant of neurotoxicity, as is the overall activity of the KP (governed by the rate-limiting enzymes IDO and TDO).

Chronic stress drives increased KP activity via elevated pro-inflammatory cytokine levels, increasing the quinolinic acid to kynurenic acid ratio and thus cytotoxic NMDA agonism (Fedele & Foster, 1993; Myint et al., 2007). In addition, quinolinic acid itself is neurotoxic, thus excess KP activity can directly induce neuronal damage (Müller & Schwarz, 2007). Increased glutamate activity in turn stimulates TNF-α release from activated microglia (Pocock & Kettenmann, 2007). A prolonged pro-inflammatory state in the CNS can therefore transition negative feedback control to a positive feedback (feed-forward) loop wherein microglia are activated and stimulate the KP, with KP metabolites promoting inflammatory activation via a shift in the balance of glutamate receptor agonism *vs*. antagonism (McNally et al., 2008). This FLT within the KP hinges on the cumulative activity of IDO (a sentinel network node), which in turn determines the quinolinic acid to kynurenic acid ratio, as shown in Figure 3A.

Additional exacerbation of the KP positive feedback loop arises over time as the cytotoxic effects of the KP reduce CNS astrocytes while microglial populations increase. Astrocytes have important protective functions (reviewed in Stapelberg et al., 2015), including secretion of neurotrophic factors such as neurotrophin-3, glial-derived neurotrophic factor and brain-derived neurotrophic factor (BDNF) (Connor & Dragunow, 1998; Cotter, Mackay, Landau, Kerwin, & Everall, 2001), and uptake of excess glutamate (McNally et al., 2008) to limit the neurotoxicity induced by excess levels of this neurotransmitter (Bezzi et al., 2004; Furuta et al., 2005).

These positive feedback motifs leading to MDD are shown in Figure 3B. With

declining CNS astrocyte populations due to excess KP activation, levels of BDNF are reduced and glutamate levels and neurotoxic KP metabolites accumulate. This in turn can lead to neuronal damage and impaired hippocampal neurogenesis, key mechanisms implicated in MDD (Pittenger, Sanacora, & Krystal, 2007; Sahay & Hen, 2008; Yirmiya & Goshen, 2011). In addition, the KP plays an important role in regulating overall tryptophan availability in the CNS (Mándi & Vécsei, 2012), thus also determining serotonin (5-HT) synthesis, as tryptophan availability is rate-limiting (Grohmann, Fallarino, & Puccetti, 2003). The KP shunts tryptophan away from 5-HT generation, which is thought to be a key mechanism in MDD (Müller & Schwarz, 2007; Stapelberg et al., 2015). Increased activity of the KP is linked to the cognitive deficits in MDD, for example (Allison & Ditor, 2014).

[Figure 3B could be placed here]

2.4 Autonomic Feedback Loops: The Sympathetic and Parasympathetic Negative Feedback Loop

The sympathetic and parasympathetic divisions of the autonomic nervous system coexist in a state of dynamic antagonism throughout the body, maintaining a dynamic equilibrium. The parasympathetic nervous system is principally comprised of the vagal nerve system, thus parasympathetic activity is frequently referred to as vagal tone (Laborde, Mosley, & Thayer, 2017). Vagal function is an important homeostatic mediator in energy regulation and physiological processes including immuno-inflammatory function. Overall autonomic control is also achieved by vagal tone acting antagonistically to sympathetic drive (e.g. Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). Porges et al. (1996) have described the 'vagal brake' - the active increase in vagal tone to inhibit sympathetic action, and conversely the reduction in vagal tone that enables increased sympathetic drive when

required.

Feedback exists between vagal and immuno-inflammatory functions, with vagal tone stimulated by immuno-inflammatory mediators, and in turn inhibits immuno-inflammatory activation. The role of the vagus in rapidly damping inflammatory responses has been termed the inflammatory reflex (Tracey, 2002), and highlights the importance of vagal function in regulating inflammatory mediators. Vagal activity triggers local release of acetylcholine (ACh), which directly inhibits release of pro-inflammatory cytokines and also indirectly suppresses their expression via stimulation of CRH secretion (Oke & Tracey, 2009).

Approximately 80% of vagal nerve fibres are sensory and the vagus is stimulated by pro-inflammatory cytokines (Olofsson et al., 2012; Thayer, 2009), allowing subsequent dampening of peripheral inflammation. A localized infection, for example, triggers a local immune response and induces vagal stimulation. This vagal stimulus inhibits pro-inflammatory cytokine release peripherally, creating a negative feedback loop that ensure the immune response is sufficiently dampened and localized, avoiding excessive tissue damage (Eskandari & Sternberg, 2002; Olofsson et al., 2012). This is shown in Figure 2A.

However, vagal tone is compromised by chronic stress, with abnormally reduced vagal tone or vagal dysfunction a key feature and potential causal factor in MDD (Rottenberg, 2007; Stapelberg, Hamilton-Craig, Neumann, Shum, & McConnell, 2012). A reduction in vagal tone impairs the functionality of the 'vagal brake', leading to increased sympathetic drive that is also characteristic of MDD (reviewed in Stapelberg et al., 2011; Stapelberg et al., 2015). Over time, a loss of vagal tone leads to chronically elevated pro-inflammatory cytokines, in turn driving dysfunction in inter-related immune, endocrine, CNS and gut systems. Loss of vagal tone also leads to chronically increased sympathetic drive. In the short term, sympathetic activation prepares the body for flight or flight via secretion of adrenaline and noradrenaline. However, chronic sympathetic drive can lead to pathologies

such as hypertension, blood coagulopathy and cardiac hypertrophy (reviewed in Stapelberg et al., 2015). The transition from vagal function to dysfunction with chronic stress thus represents a key FLT within autonomic control that broadly impacts other physiological systems.

3. Discussion

3.1 From FLTs to Critical Transition of the PINE Network - The Tipping Point To MDD

Recent large-throughput genetic studies have focussed on the question of how cells, which are subject to large numbers of complex genetic and other multi-molecular interactions, can select specific pathways or cell fates, such as differentiation or immune responses, from the multiplicity of combinatorial possibilities (e.g. Huang, Eichler, Bar-Yam, & Ingber, 2005; Tsuchiya, Giuliani, Hashimoto, Erenpreisa, & Yoshikawa, 2015). Cellular processes are governed by system attractor sets, which cause systems to converge toward a minimal energy state, drawing multiple multi-molecular interactions into a stable state (Tsuchiya et al., 2015). However, there also exists the possibility of an entire system, such as a cell, or network of regulatory physiological interactions in the body (e.g. PINE network), being pushed towards a tipping point (Scheffer et al., 2009), where the system then undergoes critical transition, following another attractor set into a new stable yet distinct state (e.g. Huang et al., 2005). Critical transitions can be driven by self-organized criticality (Tsuchiya et al., 2015). Importantly, the emergence of a convergent system solution, governed by the attractor set that influences system dynamics over a given timespan, overcomes the stochastic fluctuations that might otherwise disrupt large-scale coherent functioning of a physiological system (Tsuchiya et al., 2015).

System attractor sets are emergent properties of complex systems, underpinned by the structural organisation of constituent (e.g. physiological) networks, but largely independent of the individual pathways of those networks (e.g. Mikulecky, 2001). It can be argued that a system such as the PINE network can be viewed as a single dynamical system without examining the specific physiological role of each node in the network. The behaviours of components within such a system can collectively contribute to a 'global' critical transition - collective FLTs in physiological sub-systems of the PINE network may collectively drive the PINE network to a critical transition from health to MDD through altered feedback loop dominance (see Ford, 1999; Sterman, 2000). It is thus important to identify possible FLTs and SNNs which may contribute to a critical transition to MDD.

3.2 Use of Biomarkers to Predict Critical Transition to MDD

The physiological transitions brought about by chronic stress and which ultimately manifest as MDD are reliant on the disruption of negative feedback loops that are normally involved in homeostasis. We have detailed how FLTs can result in the emergence of pathophysiological positive feedback loops which drive abnormal elevations in CRH, cortisol, pro-inflammatory cytokines and potentially damaging products of the KP. The effects of these mediators cascade, disrupting the normal function of multiple systems, for example promoting a sympathetically driven autonomic state or disrupting glial support functions in the CNS, ultimately resulting in a critical transition to MDD. It is also evident that most of the feedback loops described are intertwined, potentiating their disruptive capacities.

The emergence of a critical system transition from health to disease, promoted by key inter-related FLTs, will be presaged by characteristic features of network instability. Complex systems exhibit early warning signs as they approach critical transitions, which can

be predictive within such systems (e.g. Scheffer et al., 2009). These early warning signs include 'critical slowing down' that can be measured by assessing recovery from perturbations; autocorrelation and an increase in variance; as well as an asymmetry of fluctuations characterized by so-called skewness and flickering (Scheffer et al., 2009). While critical transition of the entire PINE network to MDD is suggested to occur, instability of the network is hypothesised to arise in its regulatory subsystems, i.e. in the feedback loops described. Thus, we hypothesise that assessing early warning signs within feedback loops in the PINE network could theoretically predict the critical transition to MDD – possibly yielding clinical screening investigations for MDD.

Firstly, as a system approaches a critical transition, it becomes increasingly slow at recovering from small perturbations. Recovery rates from a small perturbation decrease smoothly to zero as the system approaches critical transition (Van Nes & Scheffer, 2007). One example for a method for measuring slower recovery from perturbations in the PINE network would be to assess leukocyte 5-HT_{1A} receptor expression over time. In depressed people, as compared with controls, 5-HT_{1A} receptor expression on white blood cells is inversely correlated with 5-HT activity in plasma, low platelet density, and 5-hydroxyindoleacetic acid (5-HIAA) as the excretory end-product of 5-HT metabolism. This occurs through a negative feedback mechanism affecting the HPA axis (Zhang et al., 2014). Resistance to change is described by the second derivative differential, where the rate of change in concentration of a biomarker is measured. Practically, this would require multiple measurements, which can be clinically untenable. However, leukocyte responses to the alterations in the rate of change can be measured. In this case, resistance to negative feedback inhibition and down-regulation of receptor expression is a biomarker reflecting the effect of changes in the velocity of $5HT_{1A}$ concentration pathophysiologically.

A second marker of critical transition is autocorrelation in patterns of fluctuation

within the system: autocorrelation is the repetition of a pattern over time (i.e. similarity between elements of a time series). In systems approaching a critical transition, increased autocorrelation is evident (Scheffer et al., 2009). It can be positive or negative, where there is increasing or decreasing amplitude of episodes of flickering or variance, respectively. For screening purposes, positive autocorrelation indicates that resistance to change has occurred and the biological system under analysis has changed from a negative feedback controlled system to one showing impaired control and markedly changed response to stimuli.

IL-10 is an anti-inflammatory cytokine (Oral et al., 2006), in contrast to IL-6 which is both a pro-inflammatory cytokine (Heinrich et al., 2003) and anti-inflammatory myokine (Pedersen & Febbraio, 2008). These mediators have roles in modulating neuronal plasticity (Vidal, Lemmens, Dooley, & Hendrix, 2013). Sickness behaviour, including malaise, pyrexia, social isolation, anhedonia, anorexia, loss of concentration and lethargy, has been shown to be mediated by pro-inflammatory cytokines (Dantzer, 2009). Meta-analysis confirms elevations in IL-6 and TNFα in depressed patients (Dowlati et al., 2010). Cytokines are also related to low mood in males (Chen, Lin, Chen, Mao, & Hung, 2010). Measuring IL-6 and -10 levels at different times may reveal a shift from a balanced inflammatory state (normal predominance of anti-inflammatory activity) to a pro-inflammatory state with elevations in pro-inflammatory biomarkers. It is suggested the ratio of IL-6 to IL-10 may change with an approaching critical transition to MDD. A ratio may detect such change. Thus, repeated IL-6/IL-10 ratio measures may flag a critical transition, revealing a change to a pro-inflammatory state through positive autocorrelation.

Third, systems approaching critical transition display increased variance in the pattern of fluctuations of state variables (Carpenter & Brock, 2006). Such variance could be reflected in early warning biomarkers around FLTs in the PINE network. An example of a biomarker which might reflect increased variance is HbA1c, with measurement of the area under the

curve, or integral of the average plasma glucose over the preceding 8-12 weeks, if red blood cell survival is normal. In a HbA1c measure, approximately 50% is derived from the last month and the remainder from the remaining 2 months prior to testing (Sawyer, 2015). Insulin resistance or impaired glucose tolerance, as defined by oral glucose tolerance test, fasting plasma glucose or haemoglobin $A_{1c,}$ has been clearly linked to depression (Winokur, Maislin, Phillips, & Amsterdam, 1988).

Increased variance is evident when the range of concentrations of glycated haemoglobin measured over time increases above baseline. This indicates that plasma glucose concentration is at times elevated above the normal physiologically controlled range. This variance may not be detected by measuring random plasma glucose levels as changes can be transitory, though irreversible non-enzymatic binding of glucose to the N-terminal valine amino acid on the beta globin chains on haemoglobin A occurs directly in proportion to plasma glucose concentration, providing a historic measure. As it forms a stable ketoamine over the life of the red cell, the concentration of glycated HbA1c measures those elevations. It also measures the increased variance in the plasma glucose in the area under the curve of plasma glucose concentrations over the life of that red cell.

Skewness and flickering are measures of increasing asymmetry of fluctuations before a critical transition (Scheffer et al., 2009). Skewness is a measure of the changing asymmetry of a time series probability distribution (i.e. skewness in the distribution of smaller state changes before a critical transition), which can be predictive of a critical transition (Guttal & Jayaprakash, 2008). Flickering is a related phenomenon, where a system oscillates back and forth between two opposing system basins of attraction, entering a bi-stable state before undergoing a critical transition to a single new stable state (Berglund & Gentz, 2002).

Skewness might be measured by assaying anti-thyroperoxidase (anti-TPO) antibodies, where skewness from baseline over time is the first derivative differential revealed by an

increase in anti-TPO antibodies. An increase in anti-TPO and anti-TSH receptor antibodies reveals skew from baseline over time and is the first derivative differential or change in concentration divided by change in time. A higher lifetime prevalence of depression is observed in anti-TPO antibody positive vs. negative individuals (Dufour, 2007), with a reported association between anti-TPO antibodies and lifetime diagnosis for MDD (Carta et al., 2004). Increased levels of anti-TPO antibodies suggests they might be used as a trait biomarker in MDD (van de Ven et al., 2012), and are associated with concurrent telomere shortening (Ridout, Ridout, Price, Sen, & Tyrka, 2016) suggesting recent epigenetic changes. Anti-TPO antibodies are also associated with increased risk of hypothyroidism, a known cause of MDD (Fountoulakis, Iacovides, Grammaticos, St Kaprinis, & Bech, 2004; Marangell & Callahan, 1998). Taken together, this suggests that skew above baseline in anti-TPO antibodies might be a useful clinical biomarker (within a profile) in screening for MDD.

Finally, flickering is a measure of increasing asymmetry of fluctuations over time before a critical transition, which can theoretically be captured using heart rate variability (HRV). HRV has been established as a measure of autonomic cardiac control (or cardiac vagal control) (Rottenberg, 2007) and is believed to reflect autonomic function (NASPE, 1996). However, HRV measures can reflect multiple complex physiological processes simultaneously (e.g. spectral HRV measures), which has challenged assertions of HRV being a direct or simple biomarker of autonomic function (e.g. Grossman & Taylor, 2007). Cardiac beat-to-beat time series are inhomogeneous, non-stationary, and fluctuate in an irregular and complex manner, making them suitable for non-linear measures of HRV (e.g. Ivanov et al., 2001). Systems embedded in stochastic environments may start to 'flicker' between basins of attraction for potentially alternative states before a critical transition (Dakos, van Nes, & Scheffer, 2013). Flickering could theoretically be investigated in the time series of consecutive R-wave intervals in a 24 hour cardiac recording, which may be indicative of a

critical transition in people with chronic stress that may precede MDD. Cardiac dynamics can shift between alternate states, governed by different attractors, and the complex patterns of cardiac activity which result are observable (e.g. Lerma, Krogh-Madsen, Guevara, & Glass, 2007). Application of a methodology which detects flickering might thus predict critical transitions due to underlying changes in autonomic function. Jump-drift-diffusion algorithms (Dakos et al., 2013) could be applied to the time series of consecutive R-wave intervals in a 24 hour cardiac recording. For example, Zheng, Skufca, and Bollt (2013) used the low frequency component of RR-interval data to analyse the stochastic jump with persistence around a bifurcation point, which relates to sympathetic and parasympathetic cardiac control and it is proposed that similar methodology could be used to detect a critical transition to MDD.

In summary, in progressing from one stable state to another, a system will undergo a period of instability. This instability has discernible and measurable patterns, including measures of critical slowing down, autocorrelation and increased variance, skewness and flickering in physiological regulatory systems. Critical slowing has been demonstrated in MDD in the context of fluctuations of emotional state, supporting the validity of this approach. Van de Leemput and colleagues (2014) demonstrated that elevated temporal autocorrelation, variance, and correlation between emotions in fluctuations of auto-recorded emotions were related to an increased probability of a shift between a normal mood state and MDD. The authors concluded that mood may have alternative stable states separated by critical transitions. We propose that the critical transition from the PINE physiome to the pathophysiological state of MDD (the PINE pathome) involves a series of FLTs and similar emergence of an intermediate unstable state (presented in Figures 2 and 3). Detection of FLTs and characteristic biomarkers of evolving instability can thus predict critical transition of the entire PINE network. We propose that the biomarker examples above be considered as

a linked network, reflecting interactions between feedback systems described in this paper. While changes in each biomarker could theoretically be monitored in isolation, there is additional benefit if viewed in the context of a network of biomarkers. These and other biomarkers could be used together as a suite of screening measures for MDD, detecting patterns such as temporal autocorrelation, variance or flickering before MDD sets in.

3.2 Limitations and Recommendations

Both the network model and the biomarkers presented here are putative and require experimental confirmation. This paper has sought to provide a testable hypothesis in terms of biomarkers in relation to PINE network FLTs, which might be used as a screening test for progression towards MDD. It is recommended that future work focus on testing the hypothesis that identification of key network motifs relating to feedback loops presents a list of biomarker candidates which can predict the onset of MDD in vulnerable (e.g. chronically stressed) individuals.

Furthermore, the model of feedback loops presented here is not necessarily complete, but serves rather to provide examples of FLTs which could drive a shift of the PINE network from health, through a pre-disease state followed by critical transition to the alternate stable state of MDD. Further work is required to fully map the metabolome relevant to chronic stress and MDD, and it is likely that many additional feedback loops will be identified. This paper presents concepts and a basic model which we hope that others will use as a starting point to mathematically model the PINE network. The behaviour of the whole network is likely to be more complex, especially when interactions within it are viewed over time. Such a model would require a more extensive understanding of the PINE network, statistical estimation of the governing parameters of the model and should be informed by experimental data.

There is a need to identify and map similar network motifs which extend across multiple networks (or fields of study), such as transcriptomics, proteomics and connectomics. For example, it is possible that some individuals may have a genetic predisposition which makes it easier for chronic stress to produce glucocorticoid resistance. This in turn may lead to collapse of negative feedback loops earlier or with lower stress thresholds in predisposed individuals. In a further example, TNF-α gene polymorphisms may have a role in MDD susceptibility, with depressed people having an increased frequency of the TNF2 (A) allele (Jun et al., 2003). Such predisposition may mean that pro-inflammatory states involving TNF-α are reached earlier or more readily, and also supports the stress diathesis model of MDD. Further work should reconcile such feedback loops across different network levels, with specific reference to mental disorders such as MDD and the effect on FLTs in the PINE network.

Multiple moderating factors may also influence the PINE network and potential FLTs. For example, age, sex and genetic makeup all influence responses to stress (Bekhbat & Neigh, 2017; Novais, Monteiro, Roque, Correia-Neves, & Sousa, 2017). Age has been previously discussed as a moderator in the context of the PINE network (Stapelberg et al., 2015). Gender is another important moderator, and the physiology of MDD, in terms of metabolic pathways and gender-sensitive hormone effects, may be different in men and women. Men and women exhibit differing incidences and symptoms of depression, and responses to antidepressant medication (Altemus, Sarvaiya, & Epperson, 2014; Keers & Aitchison, 2010; Parker & Brotchie, 2010; Sramek, Murphy, & Cutler, 2016), changes mirrored to some degree by studies in animal models (Dalla, Pitychoutis, Kokras, & Papadopoulou-Daifoti, 2010; Kokras & Dalla, 2017). It is thus possible that some FLTs will be sensitive to age and gender, which should be the subject of further investigation. Maternal

influences are an additional modifier, with pre-natal stress and depression known to alter stress responses, resilience and depression in adult offspring (van Bodegom, Homberg, & Henckens, 2017; Van den Bergh et al., 2017), and childhood adversity also influencing HPA axis function, stress responses and disease propensity later in life (Berens, Jensen, & Nelson, 2017; van Bodegom et al., 2017).

Lastly, recent work supports the clustering of MDD into distinct subtypes, based on latent class analysis (Lamers et al., 2010), including melancholic depression and atypical depression. These two subtypes have also been shown to have different underlying physiology, e.g. decreased HPA axis activity but increased pro-inflammatory activity in people with the atypical depressive subtype (compared to non-depressed controls), and greater HPA-axis hyperactivity and less pro-inflammatory marker activity associated with the melancholic subtype (Lamers et al., 2013). We speculate that the principles outlined in this paper around physiological FLTs are applicable to both melancholic and atypical subtypes, though the detailed physiology may be different. Further work is required to delineate these differences and further characterize the physiological networks underlying these depressive subtypes, as well as their physiological feedback loops.

Figures

Figure 1: Relationships between feedback loops, loop dominance and critical transitions in a complex biological system progressing from health to a disease state

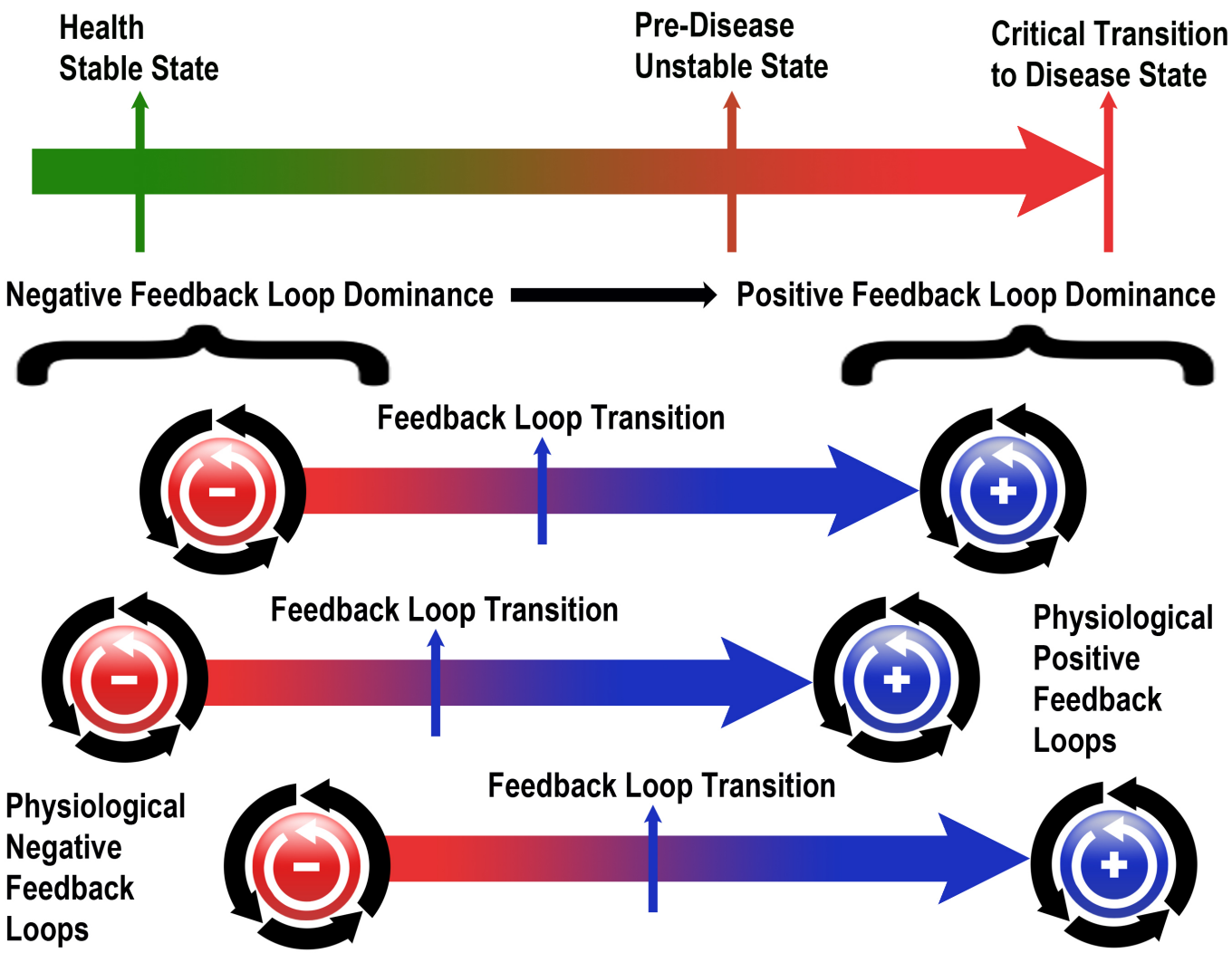
Figure 2A: Interlinked feedback loops involving endocrine, autonomic and gut microbiome pathways in the psycho-immune-neuroendocrine network during normal homeostasis

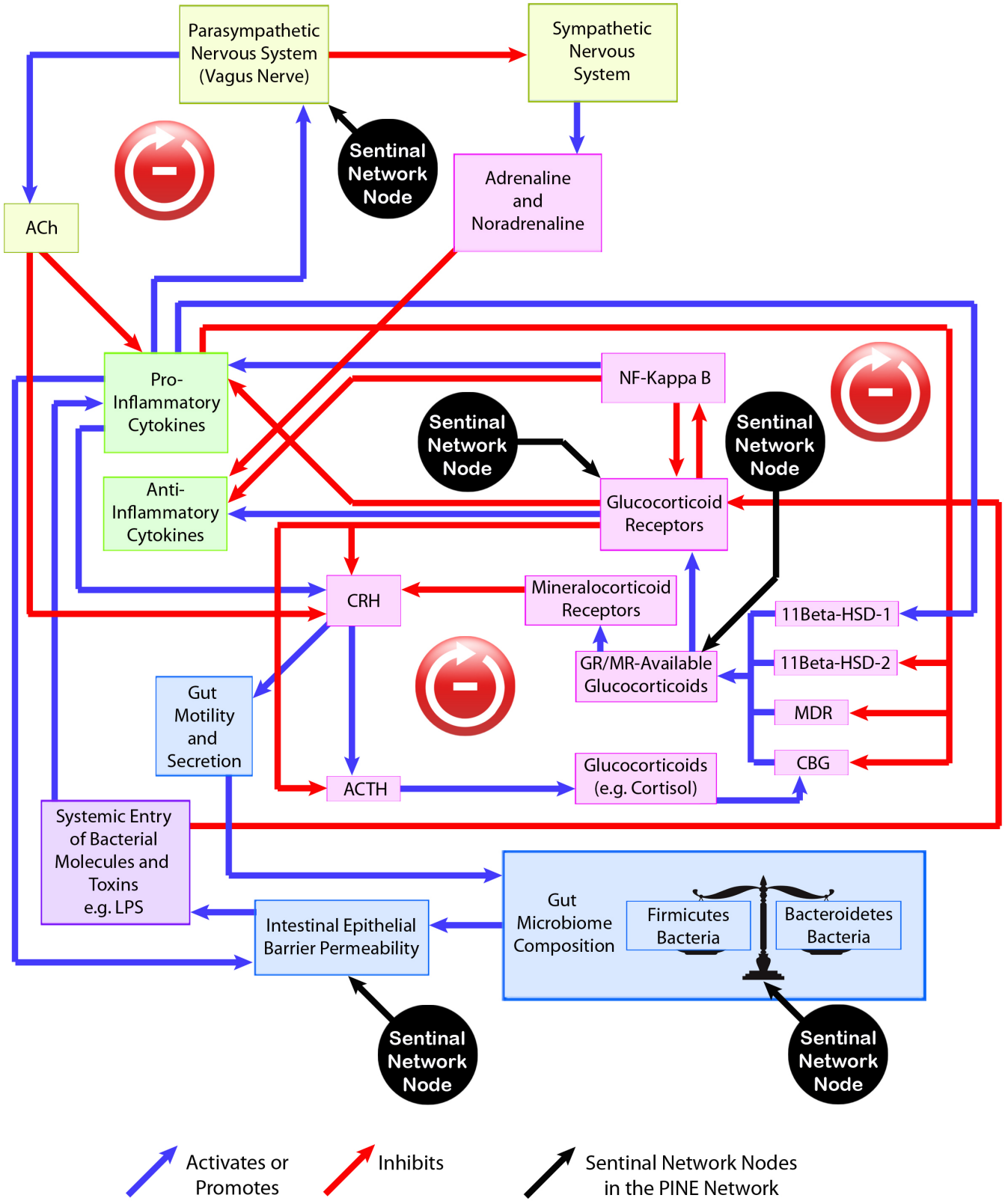
Figure 2B: Progression from negative to positive feedback loops involving endocrine, autonomic and gut microbiome pathways in the psycho-immune-neuroendocrine network

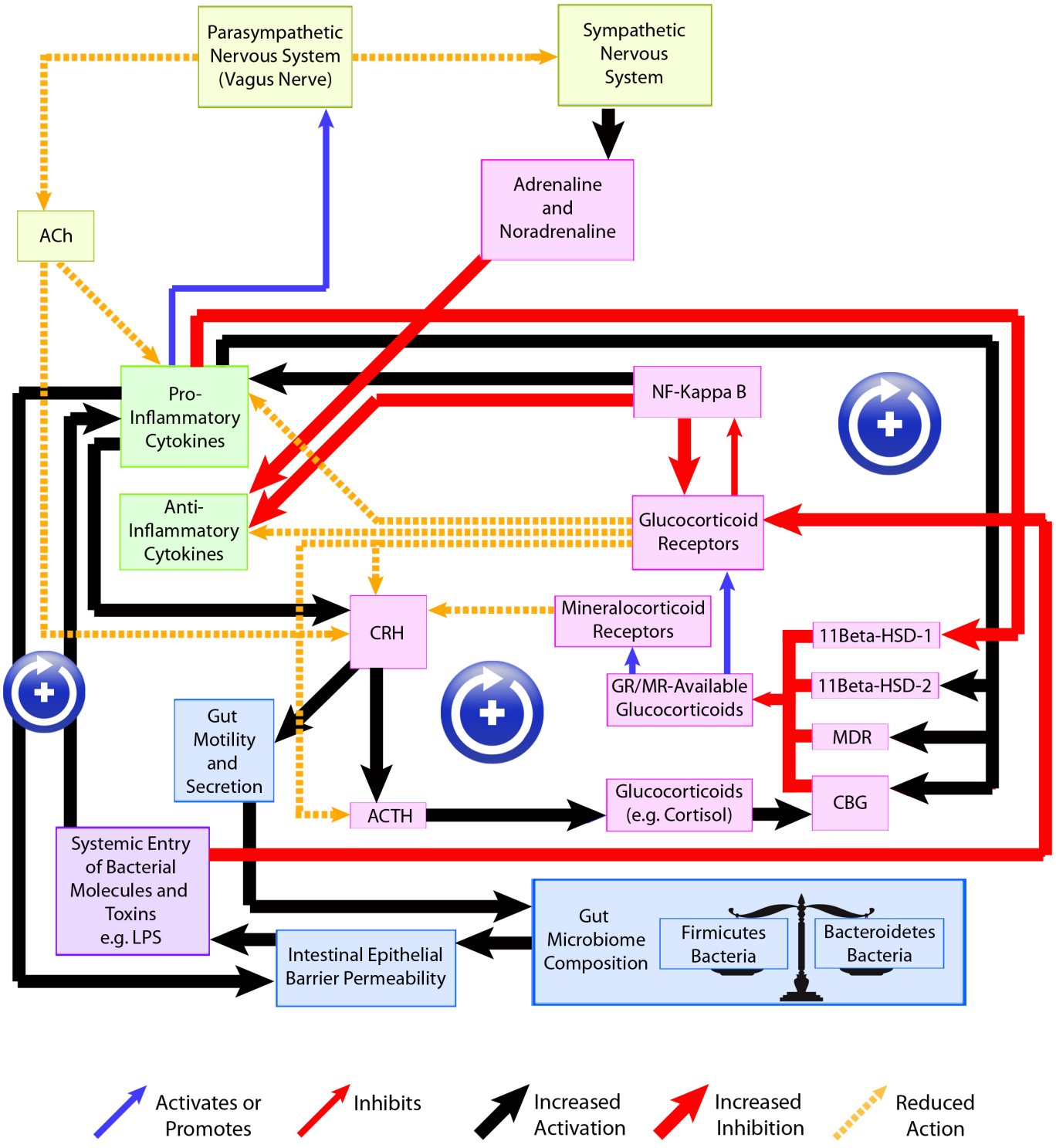
Figure 2C: Progression from negative feedback loop control of GR phosphorylation and function

Figure 3A: Interlinked feedback loops involving the kynurenine pathway in the psycho-immune-neuroendocrine network during normal homeostasis

Figure 3B: Progression from negative to positive feedback loops involving the kynurenine pathway in the psycho-immune-neuroendocrine network


Health
Stable State
Pre-Disease
Unstable State
Critical Transition
to Disease State
Negative Feedback Loop Dominance
Positive Feedback Loop Dominance
Feedback Loop Transition
Feedback Loop Transition
Physiological
Positive
Feedback
Loops
Physiological
Negative
Feedback
Loops
Feedback Loop Transition


Parasympathetic Nervous System (Vagus Nerve)
Sympathetic Nervous System
Sentinal Network Node
ACh
Adrenaline and Noradrenaline
Pro-Inflammatory Cytokines
NF-Kappa B
Sentinal Network Node
Sentinal Network Node
Anti-Inflammatory Cytokines
Glucocorticoid Receptors
CRH
Mineralocorticoid Receptors
11Beta-HSD-1
GR/MR-Available Glucocorticoids
11Beta-HSD-2
MDR
Gut Motility and Secretion
CBG
ACTH
Glucocorticoids (e.g. Cortisol)
Systemic Entry of Bacterial Molecules and Toxins e.g. LPS
Gut Microbiome Composition
Firmicutes Bacteria
Bacteroidetes Bacteria
Intestinal Epithelial Barrier Permeability
Sentinal Network Node
Sentinal Network Node
Activates or Promotes
Inhibits
Sentinal Network Nodes in the PINE Network


Parasympathetic Nervous System (Vagus Nerve)
Sympathetic Nervous System
ACh
Adrenaline and Noradrenaline
Pro-Inflammatory Cytokines
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11Beta-HSD-1
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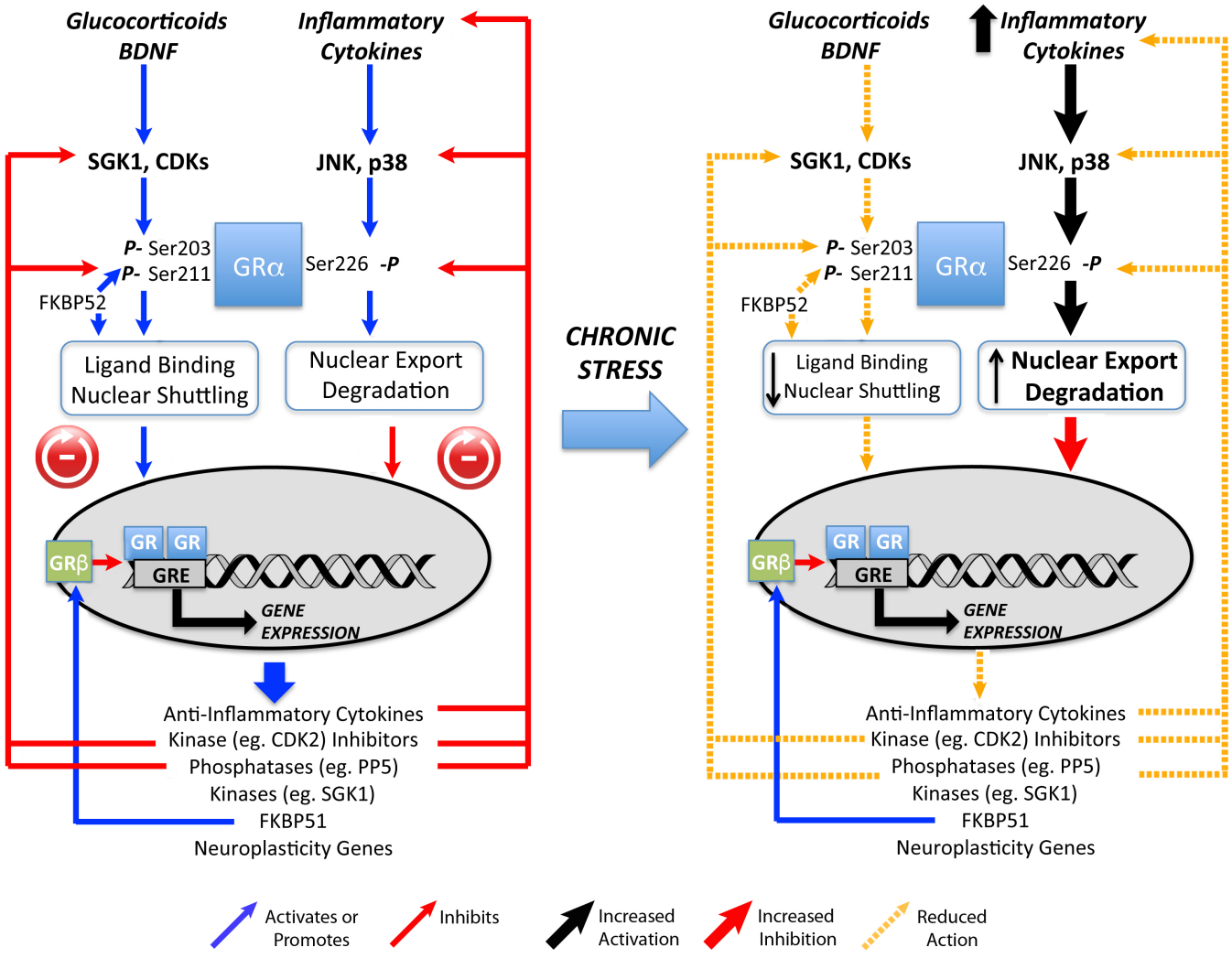
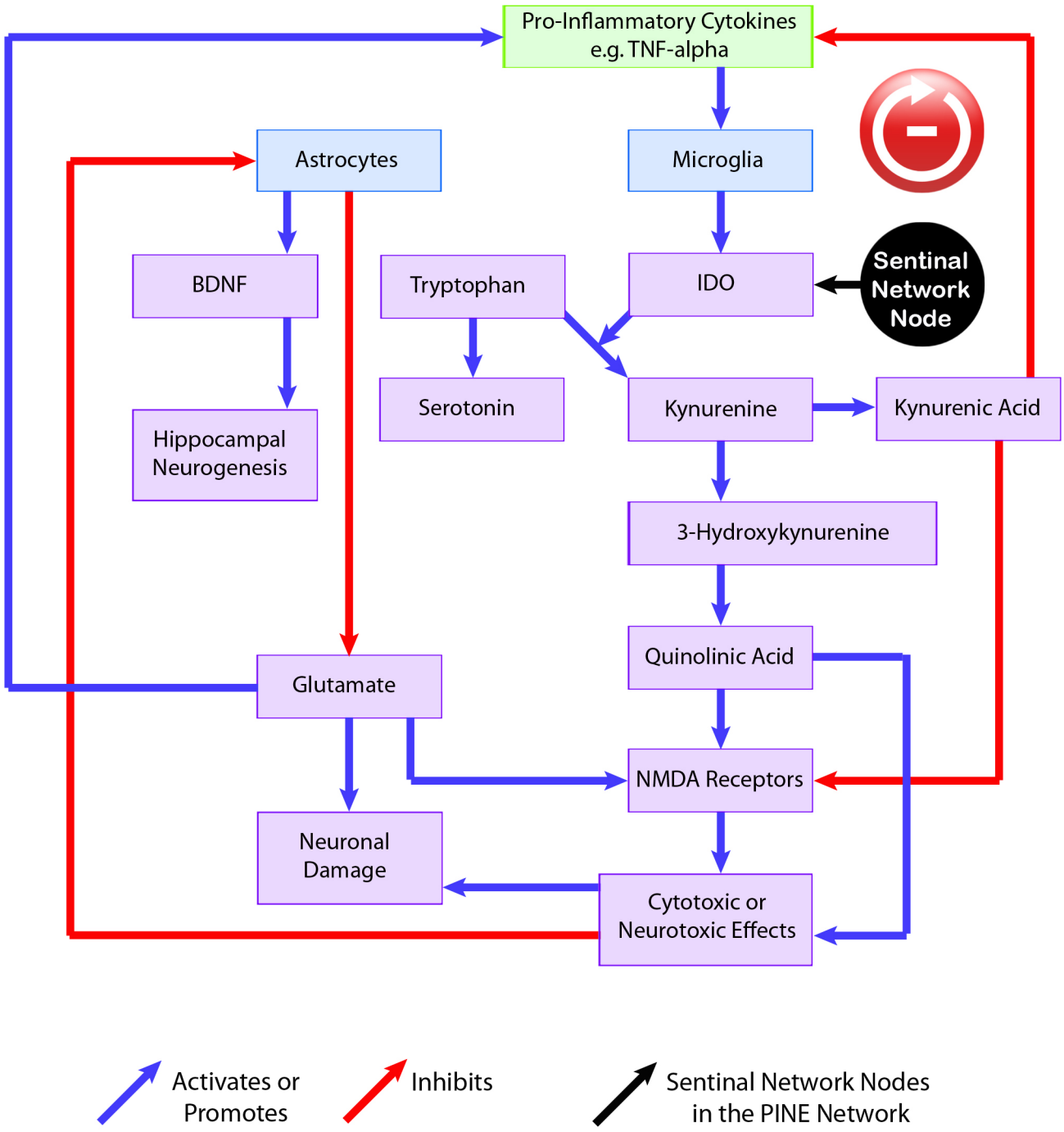
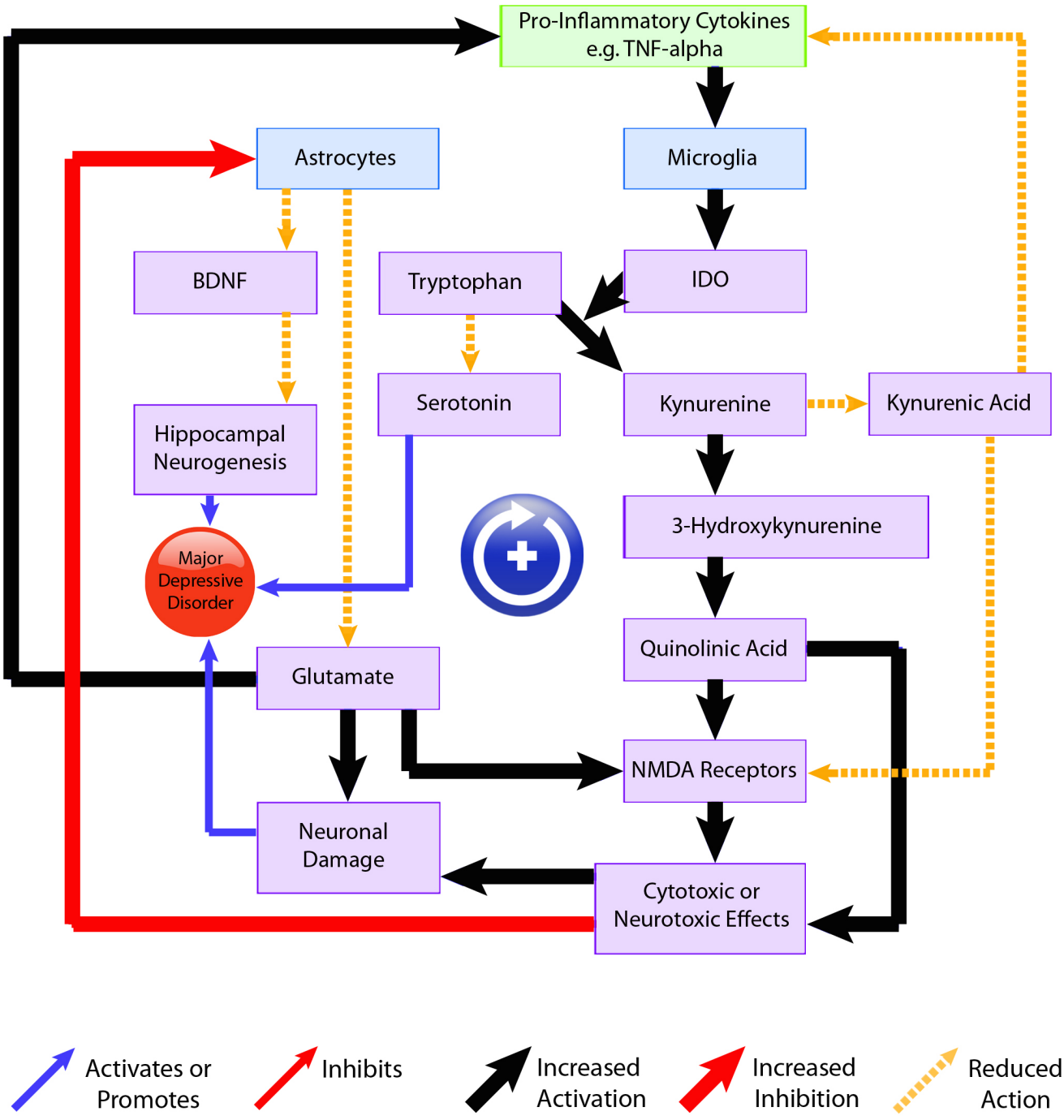
CBG
Systemic Entry of Bacterial Molecules and Toxins e.g. LPS
Gut Microbiome Composition
Firmicutes Bacteria
Bacteroidetes Bacteria
Intestinal Epithelial Barrier Permeability
Activates or Promotes
Inhibits
Increased Activation
Increased Inhibition
Reduced Action


Glucocorticoids
BDNF
Inflammatory
Cytokines
SGK1, CDKs
JNK, p38
P- Ser203
P- Ser211
GRα
Ser226 -P
FKBP52
Ligand Binding
Nuclear Shuttling
Nuclear Export
Degradation
GRβ
GR
GR
GRE
GENE
EXPRESSION
Anti-Inflammatory Cytokines
Kinase (eg. CDK2) Inhibitors
Phosphatases (eg. PP5)
Kinases (eg. SGK1)
FKBP51
Neuroplasticity Genes
CHRONIC
STRESS
Glucocorticoids
BDNF
Inflammatory
Cytokines
SGK1, CDKs
JNK, p38
P- Ser203
P- Ser211
GRα
Ser226 -P
FKBP52
Ligand Binding
Nuclear Shuttling
Nuclear Export
Degradation
GRβ
GR
GR
GRE
GENE
EXPRESSION
Anti-Inflammatory Cytokines
Kinase (eg. CDK2) Inhibitors
Phosphatases (eg. PP5)
Kinases (eg. SGK1)
FKBP51
Neuroplasticity Genes
Activates or
Promotes
Inhibits
Increased
Activation
Increased
Inhibition
Reduced
Action


Pro-Inflammatory Cytokines
e.g. TNF-alpha
Astrocytes
Microglia
BDNF
Tryptophan
IDO
Sentinal
Network
Node
Hippocampal
Neurogenesis
Serotonin
Kynurenine
Kynurenic Acid
3-Hydroxykynurenine
Quinolinic Acid
Glutamate
NMDA Receptors
Neuronal
Damage
Cytotoxic or
Neurotoxic Effects
Activates or
Promotes
Inhibits
Sentinal Network Nodes
in the PINE Network


Pro-Inflammatory Cytokines
e.g. TNF-alpha
Astrocytes
Microglia
BDNF
Tryptophan
IDO
Serotonin
Kynurenine
Kynurenic Acid
Hippocampal
Neurogenesis
3-Hydroxykynurenine
Major
Depressive
Disorder
Quinolinic Acid
Glutamate
NMDA Receptors
Neuronal
Damage
Cytotoxic or
Neurotoxic Effects
Activates or
Promotes
Inhibits
Increased
Activation
Increased
Inhibition
Reduced
Action

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